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EDITORIALS

Heart, home, and frailty: new risk scores and outcomes for cardiac surgery patients

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This editorial accompanies: Association of frailty with days alive at home after cardiac surgery: a population-based cohort study by McIsaac et al., *Br J Anaesth* 2021:126:1103–1110, doi: 10.1016/j.bja.2021.02.011

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With more than half of all patients undergoing major surgery in England more than 65 yrs of age,[1] a prevalence mirrored in other developed countries worldwide, patient frailty has become increasingly recognised as an important problem in perioperative practice. Present in 30–50% of this older cohort, frailty is a multidimensional syndrome of reduced physiological reserve resulting in vulnerability to stress (including surgical stress) that is associated with a doubled risk of mortality, major morbidity, and not being discharged home after surgery.[2] For cardiac surgical patients with frailty, these risks are magnified even further.[3]

In this issue of the *British Journal of Anaesthesia*, McIsaac and colleagues[4] report on the association between patient frailty and the outcome of days alive and at home after major cardiac surgery. This paper raises important points around measuring frailty, and identifying outcomes that are important to patients, their families, and the broader health system.

Despite a flurry of perioperative frailty research over the last decade, two major challenges persist. The first is the relative lack of literature informing associations between frailty and patient-centred outcomes after surgery, as distinct from the now commonly studied endpoints of postoperative complications and mortality.[2,5] The second, perhaps greater, challenge surrounds selecting frailty measures in perioperative care and research, to ensure that patient frailty (rather than, say, comorbidity) is specifically measured. Unfortunately, this challenge has been made more difficult by the plethora of frailty assessment scales in use: more than 50 different measurement tools have been described.[6] The perioperative literature has seen well-intentioned attempts to leverage data-rich surgical registries or administrative datasets to construct somewhat dubious frailty measures.[7] Unfortunately, many of these tools fail to actually measure frailty across the spectrum of health, which must also encompass physical performance, mobility, nutritional status, mental health, and cognition,[8] and are instead overly weighted to comorbidity as a consequence of their component variables.[7]

Determining robust outcomes that are of value to both patients and health systems has been a major challenge in perioperative medicine. After a systematic review and Delphi process, the Standardised Endpoints in Perioperative Medicine (StEP) Consensus group recommended days alive at home (DAH) as a valid patient-centred outcome.[9] DAH integrates length of hospital stay, duration of any readmission, and mortality over time,[4,10,11] typically 30 days after surgery: DAH-

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30. This is a 'more is better' metric with a skewed distribution, with the point estimate usually expressed as a median.[10,11] McIsaac and colleagues[4] calculated the DAH-30 for their primary outcome by summing all days a patient was in an acute care hospital, rehabilitation, or a continuing care/long-term facility in the 30 days after surgery, subtracting this from the number of days the individual was alive in the 30-day postoperative period. Other researchers have weighted the importance of perioperative mortality by allocating zero DAH for any patient who died during the time interval. However, this may be less appropriate for longer term (e.g. 1 yr) time periods. Further, McIsaac and colleagues examined time in subacute care, which is an important consideration for vulnerable patients.[4] Another metric related to DAH is days alive and out of hospital,[10] which only includes acute hospital care; therefore, a patient admitted to rehabilitation would be regarded as out-of-hospital, but is not at home. From a patient perspective, DAH is likely to be a more valuable metric, and has been validated in older adults (>70 yr old) after surgery,[12] but is harder to measure accurately.[11]

In their study, McIsaac and colleagues examined the association of patient frailty, measured via a preoperative frailty index (pFI), with DAH after major cardiac surgery.[4] Among 61 000 patients, each 10% increase in the frailty index was associated with a 2.4-day decrease in adjusted median DAH in the first month, and a 4.3-day decrease in the first year after surgery. Mediation analyses were also performed, which helped delineate the relative contributors to this reduction in DAH. Although mortality was the major factor at 1 yr postoperatively, accounting for 62% of the frailty-DAH association, only 6% of this association was mediated by mortality in the 30 days after surgery. Instead, discharge to other than home and prolonged hospital length of stay were more important factors in mediating early reductions in time at home for patients with frailty. The magnitude of this (adverse) reduction in DAH in the month after surgery was considerable, as the authors point out, on par with the attributable difference of a 30-yr increase in patient age, or of an ASA physical status of 4 *vs* 2.

The choice of frailty instrument is a crucial consideration in perioperative research. Many frailty tools, especially those derived from health administrative datasets, are limited by the combination of a simplistic approach to defining frailty, inclusion of too few variables, missingness, and overreliance on comorbidity measures as surrogates for the more comprehensive frailty syndrome.[7] In this manner, McIsaac and colleagues are to be congratulated on their choice of a frailty tool with high face- and construct-validity. Although still heavily weighted towards medical conditions, the inclusion in the pFI of non-comorbidity health deficits relevant to the frailty syndrome (such as supported living environment, weight loss, falls) is appropriate. The pFI also encompasses more than 30 health deficits, a requirement for a sufficiently broad and reproducible frailty index.[13] Notably, the majority of variables in the benchmark Rockwood 70-item frailty index, on which many subsequent frailty tools have been modelled, are non-medical comorbid conditions.[14] Some non-health related variables in McIsaac and colleagues' model are perhaps more questionable inclusions in their pFI, such as patient socioeconomic status and drug/alcohol abuse. There is ongoing controversy among frailty researchers about whether such social factors (as distinct from health deficits) should be included in a frailty measure.[15] Although they do increase vulnerability to adverse outcomes, such social attributes may not contribute to frailty *per se*, and probably do not warrant incorporation in a frailty index comprised of health deficits.

McIsaac and colleagues' ability to construct a frailty index from integration of multiple datasets is noteworthy, as this increases the number and breadth of variables across the spectrum of health available for inclusion. In contrast, the most reported measure used in perioperative studies, the National Surgical Quality Improvement Program 'modified frailty index' (mFI) includes only 11 variables, nine of which are medical conditions, with resultant concerns about whether this in fact classifies frailty or not.[7] A slightly alternative methodology in frailty index construction is the use of granular patient-level data obtained from the hospital admission process, as distinct from administrative databases.[5,16] The advantage of this approach is better coverage of non-comorbidity specific health variables, with promising initial validation work in surgical cohorts,[16] however, further research is required to see whether this approach is feasible to deploy in the measurement of frailty at the population scales seen in this study.

A major additional limitation of frailty indices constructed using administrative datasets is vulnerability to missing data. This has proved a significant drawback to the mFI since 2011, when reporting of some variables was made optional, two subsequent studies finding 100% missing data rates affecting at least five of 11 variables.[17,18] It is notable, then, that McIsaac and colleagues found no missing values present in pFI construction for their 61 000 patients; an incredible achievement. Importantly, they have also previously modelled the effect of a 15% missing variable rate, finding minimal impact on pFI model accuracy.[19] We can thus be even more confident about the pFI construct used in this study. Furthermore, the authors also adjusted for factors that are known to be associated with (but not causative of) frailty, such as age, surgery type, and surgical urgency. The interplay between advancing patient age, greater frailty degree, and greater likelihood of emergency *vs* elective surgery is complex, and can easily confound associations with negative postoperative outcomes. It is thus reassuring to see that findings with frailty were consistent after adjusting for these variables.

The other major advantage of the pFI developed by McIsaac and colleagues is the ability to classify different degrees of frailty, unlike almost all other frailty scales used perioperatively (e.g. the Johns Hopkins Adjusted Clinical Groups[20]), which either dichotomise frailty as present or absent, or classify at most three categories. This allows granular assessment for frailty beyond that of a binary variable, which is increasingly recognised as important for acute risk stratification in areas as diverse as perioperative practice to decisions about ICU triage.[21,22]

This study adds important new knowledge to our understanding of outcomes for patients with frailty presenting for major surgery. Although quality of life (QoL) endpoints are increasingly reported in the perioperative literature, a 2016 systematic review of frailty and postoperative outcomes found QoL assessed in only one of 23 studies.[2] The association between frailty and postoperative QoL appears complex, with some studies suggesting poorer outcomes after surgery in patients with frailty,[23] and others reporting QoL improvement.[24] This study by McIsaac and colleagues adds to our understanding of how frailty affects one very important QoL measure: time spent at home after surgery.[4] Further research is required to inform how frailty influences the other relevant postoperative patient-centred endpoints identified by the StEP group: patient satisfaction, health-related QoL, functional status, and life-impact measures.[9]

A further consideration when assessing the importance of DAH is whether patients were living in their own home before surgery. Non-home dwelling preoperative location, more common with higher degrees of frailty,[16,25] will by definition result in fewer DAH after surgery. Other studies have illustrated this distinction, between non-home and *new* non-home discharge, as a result of patients who lived in residential care before hospitalisation.[25,26] As such, not only how, but *where*, patients with frailty were living before surgery becomes important when assessing endpoints such as DAH. Although this important relationship between preoperative patient residential location, frailty, and DAH was not explored in McIsaac and colleagues' study,[4] non-home dwelling patients were presumably uncommon in their cohort, who were presenting for coronary artery bypass, cardiac valve surgery, or both. This limitation of DAH as an endpoint for patients with frailty must, however, be considered in future perioperative frailty research. Restricting this study's population to cardiac surgical patients may also limit the wider generalisability of the finding of a reduction in DAH associated with frailty, as cardiac surgery may necessitate prolonged durations of hospital stay, with additional discharge to rehabilitation for some patients. Further work is thus required to establish if the same magnitude of reduction in DAH because of frailty is observed in different surgical cohorts or among patients with frailty undergoing more minor operations. Conversely, a greater adverse reduction in DAH might be expected for some surgery types, such as patients undergoing care for fractured neck of femur.

In conclusion, McIsaac and colleagues[4] are to be congratulated on an ambitious and novel study. As anaesthetists, perioperative physicians and surgeons are increasingly called on to manage the complex issues associated with frailty in coming years, it is imperative that we not only understand how to measure frailty, but how to measure what is important to patients with frailty. Further, we need to be able to link the two for assessing and communicating risks for frail patients in the perioperative journey. The risk of being unable to return home after surgery, a worry for many patients undergoing anaesthesia, is among the greatest concerns for this most vulnerable patient group.

Authors' contributions

Editorial design, writing and revision of manuscript: JND, DAS
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Declarations of interests

The authors declare that they have no conflicts of interest.

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Anaesthesia, neural activity, and brain development: interneurones in the spotlight

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Developing brain networks are particularly receptive to acquiring certain kinds of information and even need those instructive signals for their continued functional assembly. Information input is commonly translated into neural activity driven primarily by GABAergic and glutamatergic neurotransmission. During critical periods of neural development, the timing and duration of neural activity patterns in maturing brain circuitry sculpt function, and even short interference with physiological activity patterns can trigger long-term functional consequences.[1] In this context, and as anaesthetics are major pharmacological modulators of neural activity, it is not surprising that experimental data in animals convincingly raise the plausibility for persistent behavioural and cognitive alterations after exposure to anaesthetics in early postnatal life.[2] Although the human relevance of these laboratory observations remains debated, manipulating neural activity with general anaesthetics during brain development provides us with an extraordinary experimental tool to study critical-period neural plasticity. Indeed, deciphering molecular, cellular, and network mechanisms underlying the effects of anaesthesia exposure on immature brain networks may provide us with a better understanding of the context-dependent modulation of neural plasticity. In addition to advancing academic knowledge, this line of research may also lead us to develop therapeutics, where general anaesthetics could be used as modulators of pathological plasticity states, an exciting concept that goes beyond the current use of these drugs to provide a rapidly reversibly state of unconsciousness.[3]

In this issue of the *British Journal of Anaesthesia*, Zhou and colleagues[4] provide thought-provoking new information about the long-term impact of early-life anaesthesia exposure on developing neural networks. In line with some previous laboratory observations, the authors first show that repeated (but not single) exposures of neonatal mice to propofol induce long-term behavioural, cognitive, and motor impairments in these animals, and that these functional deficits are associated with a decrease in the number of pyramidal neurones and excitatory synaptic contacts in the cerebral cortex. Administered the unconventional non-competitive gamma-aminobutyric acid type A ($GABA_A$) receptor agonist pentylenetetrazol or the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor agonist CX546 to mice recovering from anaesthesia, they found that these treatments, aimed to accelerate recovery of physiological patterns of neural activity, protected against the long-term effects of propofol exposure. Using a combination of genetic cell labelling methodologies and sophisticated *in vivo* neuronal imaging

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